(54)   **METHOD AND APPARATUS FOR INTERPRETING DNA MICROARRAY PATTERNS**

VERFAHREN UND VORRICHTUNG ZUR INTERPRETATION VON
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INTERPRETATION DE MOTIFS DE JEUX ORDONNES DE MICROECHANTILLONS D'ADN
BIONIQUE HYBRIDE PAR DYNAMIQUE REVERBEREE CONVERGENTE
AUTO-ECHELONNANTE, ET DISPOSITIF A CET EFFET

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Description

Field of the Invention

5   [0001]   The invention generally relates to techniques for analyzing biological samples, such as DNA or RNA samples, and in particular to techniques for analyzing the output of a hybridized biochip to which the sample has been applied.

Background of the Invention

10   [0002]   A variety of techniques have been developed to analyze DNA, RNA samples or other biological samples to identify diseases, mutations, or other conditions present within a patient providing the sample. Such techniques may determine, for example, whether the patient has any particular disease such as cancer or AIDS, or has a genetic predisposition toward the disease.

[0003]   One particularly promising technique for analyzing biological samples uses a DNA biochip (or microarray)
15   which generates a hybridization pattern representative of the characteristics of the DNA within the sample. Briefly, a DNA microarray includes a rectangular array of single stranded DNA fragments. Each element within the array includes millions of copies of identical single stranded strips of DNA containing specific sequences of bases. A different fragment of DNA may be provided at each different element of the array. In other words, location (1,1) contains a different single stranded fragment of DNA than location (1,2) which also differs from location (1,3) etc.

20   [0004]   A DNA sample to be analyzed is first fragmented into individual single stranded sequences with each sequence being tagged with a fluorescent molecule. The fragments are applied to the microarray where each fragment bonds only with matching DNA fragments already embedded on the microarray. Fragments which do not match any of the elements of the microarray simply do not bond at any of the sites of the microarray and are discarded. Thus, only those microarray locations containing fragments that match fragments within the DNA sample will receive the
25   fluorescent molecules. Typically, a fluorescent light source is then applied to the microarray to generate a fluorescent image identifying which elements of the microarray bonded with fragments of the DNA sample and which did not. The image is then analyzed to determine which specific DNA fragments were contained within the original sample and to determine therefrom whether particular diseases, mutations or other conditions are present within the DNA sample.

[0005]   For example, a particular element of the microarray may be provided with fragments of DNA representative
30   of a particular type of cancer. If that element of the array fluoresces under fluorescent illumination, then the DNA of the sample contains the DNA sequence representative of that particular type of cancer. Hence, a conclusion can be drawn that the patient providing the sample either already has that particular type of cancer or is perhaps predisposed towards that cancer. As can be appreciated, by providing a wide variety of known DNA fragments on the microarray, the resulting fluorescent image can be analyzed to identify a wide range of conditions.

35   [0006]   Unfortunately, under conventional techniques, the step of analyzing the fluorescent pattern to determine the nature of any conditions characterized by the DNA is expensive, time consuming, and somewhat unreliable for all but a few particular conditions or diseases. FIG. 1 illustrates various conventional techniques for analyzing the flourescent pattern. Some prior art systems utilize two or more of the techniques. It should be noted though that many combinations of the techniques are not provided in the prior art. Briefly, the fluorescent pattern is quantized to yield a dot spectrogram
40   at step 10. Any of four different techniques are employed to identify oligonucleotides represented by the dot spectrogram and to then identify mutations based upon the oligonucleotides. More specifically, the dot spectrogram may be analyzed using a trained neural network recognizer 12, a statistical decision theory recognizer 14, a fuzzy/expectation method (EM) clustering algorithm 16 or a rule-based inferencing/truth table search 18.

[0007]   The results are interpreted to yield mutations of interest at step 20. Then the mutations are again processed
45   using either a trained neural network recognizer 22, a statistical decision theory recognizer 24, a fuzzy/EM clustering algorithm 26 or a rule-based inferencing/truth table search 28. The results are combined at step 30 to yield a diagnosis.

[0008]   Finally, disease confirmation is performed at step 32 by "reduction", in other words the disease is confirmed by probabilistic inferencing.

[0009]   One major problem with many conventional techniques is that the techniques have poor repeatability. Hence,
50   if the same sample is analyzed twice, different results are often obtained. Also, the results may vary from lab to lab. Also, skilled technicians are required to operate the DNA microarrays and to analyze the output resulting in high costs. One reason that repeatability is poor is that the signatures within the dot spectrogram that are representative of mutations of interest are typically very weak and are immersed in considerable noise. Conventional techniques are not particularly effective in extracting mutation signatures from dot spectrograms in low signal to noise circumstances.

55   [0010]   Accordingly, it would highly desirable to provide an improved method and apparatus for analyzing the output of the DNA microarray to more expediently, reliably, and inexpensively determine the presence of any conditions within the patient providing the DNA sample. It is particularly desirable to provide a technique that can identify mutation signatures within dot spectrograms even in circumstance wherein the signal to noise ration is extremely low. It is to

these ends that aspects of the invention are generally drawn.

[0011] One analysis technique for achieving the aforementioned advantages is described in U.S. Patent 6,136,541 entitled "Method and Apparatus for Interpreting Hybridized Biochip Patterns Using Resonant Interactions Employing Quantum Expressor Functions". Briefly, the method of the co-pending application operates as follows. The method identifies mutations, if any, present in a biological sample from a set of known mutations by analyzing a dot spectrogram representative of quantized hybridization activity of oligonucleotides in the biological sample to identify the mutations. A resonance pattern is generated which is representative of resonances between a stimulus pattern associated with the set of known mutations and the dot spectrogram. The resonance pattern is interpreted to yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations. In a particular example described in the co-pending application, the resonance pattern is generated by iteratively processing the dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The resonance pattern is then analyzed to a yield a set of confirmed mutations by mapping the confirmed mutations to known diseases associated with the pre-selected set of known mutations to identify diseases, if any, indicated by the DNA sample. A diagnostic confirmation is then made by taking the identified diseases and solving in reverse for the associated Quantum Expressor Functions and then comparing those Quantum Expressor Functions with ones expected for the mutations associated with the identified disease to verify correspondence. If no correspondence is found, a new sub-set of known mutations are selected and the steps are repeated to determine whether any of the new set of mutations are present in the sample.

[0012] By exploiting a resonant interaction, mutation signatures may be identified within a dot spectrogram even in circumstances involving low signal to noise ratios or, in some cases, negative signal to noise ratios. By permitting the mutation signatures to be identified in such circumstances, the reliability of dot spectrogram analysis is thereby greatly enhanced. With an increase in reliability, costs associated with performing the analysis are decreased, in part, because there is less of a require ment for skilled technicians. Other advantages of the invention arise as well.

[0013] Although the method of the co-pending application represents a significant advance over techniques of the prior art, room for further improvement remains. In particular, it would be desirable to enhance the method of the co-pending application to achieve a higher degree of repeatability.

[0014] In particular, repeatability is affected by spatio-temporal degradation of hybridization in DNA microarrays implementing both passive and active hybridization. In bioelectronic systems implementing passive hybridization, sources affecting repeatability of analysis results include:

- Stochastic variability in chemical kinetics
- Immobilized oligonucleotide damage during fabrication
- Uneven kinetics during thermally facilitated fluidics reaction
- Post hybridization thermal degradation. Currently biochips are "amplification limited".

This is in large part due to losses during high-termperature hybridization downstream. During periods when the sample temperature changes from high to low or low to high, extraneous, undesirable reactions can occur that consume important reagents and create unwanted and interfering chemicals. Rapid transitions ensure that the sample spends a minimum of time at undesirable intermediate temperatures, so that the amplified DNA product has optimum fidelity and purity. So current methods rely on excessive amplification to compensate for these losses.

- Oligonucleotide entanglement
- Environmental decoherence due to energy and radiation
- Uneven fluidic catalysis
- Unstable fluorescence and chemiluminiscence marker binding
- Spontaneous emissions
- Partial bindings
- Anti-aliasing during readout and digitization

[0015] Active hybridization is degraded by

- Capacitive coupling between elements of the immobilized matrix
- Partial bindings due to current leakage and uneven conductance
- Ultrascale quantum squeeze effects
- Spontaneous emission
- Nonspecific oligonucleotide trapping

- Chaotic relaxation across the array

[0016] Hence, aspects of the present invention are directed, in part, to providing enhanced repeatability of biological sample analysis despite these factors.

Summary of the Invention

[0017] In accordance with the invention, a method according to claim 1 is provided for identifying mutations, if any, present in a biological sample. The method operates to analyze an arrayed microdevice output pattern generated using the sample to identify the mutations in the sample. In accordance with the method the output pattern is tessellated. A stimulus pattern associated with the set of known mutations is generated. A resonance pattern is then generated which is representative of resonances between the stimulus pattern and the tessellated output patterns. The resonance pattern is interpreted to yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations.

[0018] In an exemplary embodiment, the output pattern is a dot spectrogram representative of quantized hybridization activity of oligonucleotides in a DNA sample. The stimulus pattern is generated based upon Quantum Expressor Functions. The dot spectrogram is tessellated to match morphological characteristics of the Quantum Expressor Functions and local parametrics are extracted. The tessellated dot spectrogram and the stimulus pattern are transformed to a metrically transitive random field via phase shifting. The resonance pattern is generated by iteratively processing the tessellated dot spectrogram by performing a convergent reverberation to yield a resonance pattern representative of resonances between the Quantum Expressor Functions and the tessellated dot spectrogram until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations. The convergent reverberation includes the step of performing a convergent reverberant dynamics resonance analysis of the tessellated dot spectrogram using the resonance stimulus pattern to identify mutations represented by the tessellated dot spectrogram. The convergent reverberation also includes the step of performing a convergent reverberant dynamics resonance analysis of the mutations using the resonance stimulus pattern to identify diagnostic conditions represented by the mutations.

[0019] Also in the exemplary embodiment, the convergent reverberant dynamics resonance analyses are performed by determining resonance dynamics relaxation values based upon the tessellated dot spectrogram and the resonance stimulus; filtering the dynamics relaxation values using ensemble boundary and complete spatial randomness (CSR) filters to yield a second set of values; applying bulk property estimators to the dynamics relaxation values to yield a third set of values; evaluating the second and third sets of values to determine a degree of resonance convergence; and then determining from the degree of resonance convergence whether a paralysis of dynamics has occurred and, if so, repeating the aforementioned steps.

[0020] In the exemplary embodiments, by tessellating the dot spectrogram to match morphological characteristics of the Quantum Expressor Functions and by exploiting a resonant interaction employing a resonance convergence check which uses extracted tessellation parametric, mutation signatures may be identified within a dot spectrogram with a high degree of repeatability. By achieving a high degree of repeatability, the reliability of dot spectrogram analysis is thereby greatly enhanced. With an increase in reliability, costs associated with performing the analysis are decreased, in part, because there is less of a requirement for skilled technicians. Other advantages of the invention arise as well.

[0021] Among other applications, principles of the invention are applicable to the analysis of various arrayed biomolecular, ionic, bioelectronic, biochemical, optoelectronic, radio frequency (RF) and electronic microdevices. Principles of the invention are particularly applicable to mutation expression analysis at ultra-low concentrations using ultra-high density passive and/or active hybridization DNA-based microarrays. Techniques implemented in accordance with the invention are generally independent of the physical method employed to accumulate initial amplitude information from the bio-chip array, such as fluorescence labeling, charge clustering, phase shift integration and tracer imaging. Also, principles of the invention are applicable to optical, optoelectronic, and electronic readout of hybridization amplitude patterns. Furthermore, principles of the invention are applicable to molecular expression analysis at all levels of abstraction: namely DNA expression analysis, RNA expression analysis, protein interactions and protein - DNA interactions for medical diagnosis at the molecular level.

[0022] Apparatus embodiment according to claim 28 is also provided.

Brief Description of the Drawings

[0023] The features, objects, and advantages of the present invention will become more apparent from the detailed description set forth below when taken in conjunction with the drawings in which like reference characters identify correspondingly throughout and wherein:

FIG. 1 is a flow chart illustrating exemplary techniques for analyzing dot spectrograms, some combinations of which are in the prior art.

FIG. 2 is a flow chart illustrating an exemplary method for analyzing the output of a hybridized DNA microarray biochip in accordance with the method of the co-pending application.

FIG. 3 is a flow chart illustrating exemplary enhancements to the method of the co-pending application provided in accordance with the present invention.

FIG. 4 is a flow chart illustrating an exemplary method for analyzing the output of a hybridized DNA microarray in accordance with the method of the present invention.

Detailed Description of Exemplary Embodiments

[0024] With reference to the remaining figures, exemplary embodiments of the method of the co-pending application and of the present invention will now be described. The exemplary methods will be described primarily with respect to the analysis of mutation signatures within output patterns of DNA biochip microarrays, but principles of the invention to the analysis of a wide variety of other patterns as well.

Overview of Co-Pending Application

[0025] Briefly, the exemplary method of the co-pending application exploits, among other features: (a) a novel representation, interpretation and mathematical model for the immobilized oligonucleotide hybridization patterns, represented via a dot spectrogram; (b) a new "active" biomolecular target detection and discrimination method based on quantum resonance interferometry, and (c) a new spatial hashing function that yields accurate diagnostic assessment.

[0026] To this end the exemplary method of the co-pending application exploits a fundamentally different computational paradigm for mutation expression detection in pre-enhanced dot spectrogram realizations. The method is an innovative modification to dynamically arrayed quantum stochastic resonance (QSR) for discrete system analysis. The arraying strategy is a function of the expression pathway of interest. The method depends on the molecular diagnostic spectrum being addressed. Banks of coupled quantum resonators are algorithmically designed to significantly enhance signal-to-noise (SNR) performance and fuse multiple synthetic renormalized dot spectrogram realizations to better detect prespecified biomolecular expression patterns.

[0027] Moreover, the exemplary method of the co-pending application exploits an enhancement in previous extensions to classical stochastic resonance (SR) and array enhanced SR (AESR) in signal processing and sensor data analysis. Stochastic resonance is a phenomenon wherein the response to a sensor, modeled in terms of a bistable nonlinear dynamical system, is enhanced by applying a random noise element and a periodic sinusoidal forcing function. SR occurs when the SNR passes through a maximum as the noise level is increased.

[0028] Thus as important aspect of the exemplary method of the co-pending application involves the coupling of transformed and preconditioned discrete microarray outputs to a mathematical model for a quantum-mechanical dynamical system with specific properties. When driven in a particular manner, the coupled system exhibits a nonlinear response that corresponds to detection of phenomena of interest. The method exploits modulation of observables from a "base" (canonical continuous dynamical system), so that a selected set of spectral properties match a similar selected spectral properties of a discrete spatial tessellation substructure from an amplitude spectrogram derived from bioelectronic observables. The method further exploits the concept of convolving a discrete spatial system (derived from base mutants of interest) with a continuous asymmetric temporal system to derive a spatiotemporal input to further convolve with another discrete spatial projection (of an inherently partially stabilized spatiotemporal system).

[0029] Hence key components of the exemplary biomolecular detection method of the co-pending are: (i) selection of a basis system; (ii) generation of designer Quantum Expressor Function (QEF) for coupling with the substrate to be analyzed; (iii) generation of a Hamiltonian to describe relaxation dynamics of the coupled system; (iv) modulation of resonance parameters to enforce early resonance; (v) and exploitation of resonance suppressors to verify detection.

[0030] Referring to FIG. 2, initially at step 100, a set of mutations of interest are selected. The mutations, for example, may be mutations relevant to cancer, AIDS, or other diseases or conditions. At step 101, preconditioner transforms are generated based upon the selected set of mutations. The preconditioner transforms are provided to convert mutation nucleotide sequences into expected amplitude patterns in the prespecified microarray representation, given a particular biochip layout. At step 102, Quantum Expressor Functions are generated based upon the Hamiltonian of a pre-selected basis system. The Quantum Expressor Functions are designed to couple the Hamiltonian for the selected basis system to a predetermined DNA microarray configuration to permit a resonance interaction involving the output of the DNA microarray. Resonance stimulus is generated, at step 106, using the Quantum Expressor functions.

[0031] What has been summarized thus far are preliminary steps performed off-line for setting up the Quantum Expressor Functions and the corresponding resonance stimulus. These steps need be performed only once for a given set of mutations and for a given DNA microarray configuration. Thereafter, any number of output patterns from the

DNA microarray may be processed using the Quantum Expressor Functions to identify whether any of the mutations of the pre-selected set of mutations are found therein. Preferably, Quantum Expressor Functions are pre-generated for a large set of mutations and for a large set of DNA microarray patterns such that, for each new DNA microarray output pattern from each new patient sample, the presence of any of the mutations can be quickly identified using the predetermined set of Quantum Expressor Functions. In general, the aforementioned steps need be repeated only to update the Quantum Expressor Functions to accommodate new and different DNA microarray patterns or to if new mutations of interest need to be considered.

[0032] At step 106, an output pattern (referred to herein as a Dot Spectrogram) is generated using a DNA microarray for which Quantum Expressor Functions have already been generated. At step 108, the dot spectrogram is preconditioned to yield a dot spectrogram tesselation (DST) to permit exploitation of a resonance between the dot spectrogram and the Quantum Expressor Functions. The actual resonant interaction, which involves convergent reverberations, is performed at step 110 until a pre-determined degree of convergence is achieved. Once convergence is achieved, a resulting resonance pattern is processed at step 112 to identify any mutations represented thereby. As will be described below, step 112 is rendered trivial by virtue of the aforementioned resonant interaction which is based upon Quantum Expressor Function already correlated with the pre-selected mutations. Hence, no complicated analysis is required to interpret the resonance pattern to identify the mutations. Next, at step 114, the mutations are mapped to corresponding diseases and conditions to thereby identify any diseases or conditions that the patient providing the sample being analyzed is afflicted with. Again, this is a fairly trivial step. Finally, at step 116, diagnostic confirmation is preformed to verify that the diseases or conditions are present in the sample. This is achieved by starting with the found diseases or conditions and then performing the steps of the method in reverse.

[0033] Each of the aforementioned steps are described in detail in the co-pending application and the detailed description thereof is not repeated herein.

Overview of the Exemplary Method of the Present Invention

[0034] The present invention is directed, in part, to improving the repeatability of the method of the co-pending application by tessellating the dot spectrogram so as to match morphological characteristics of the Quantum Expressor Functions and by using extracted local parametrics as part of a resonance convergence check during the resonance interaction. These additional steps have the advantage of establishing uncertainty bounds which permit method repeatability to be enhanced and quantified.

[0035] FIG. 3 illustrates enhancements to the technique of FIG. 2 provided by the present invention along with steps of the technique of FIG. 2. The repeated steps of FIG. 2 appearing in FIG. 3 may be the same as those of FIG. 2 and will not be redescribed. Like reference numerals, incremented by one hundred, are employed to represent the repeated steps.

[0036] Briefly the enhancements of the present invention entail five major steps:

- Preconditioning the hybridized array output pattern (i.e. the dot spectrogram) by a fuzzy tessellation and coupling the preconditioned output pattern with a canonical system with aftereffect and memory properties (step 218);
- Estimation of amplitude wanderings or dispersion (step 220);
- Implementation of resonance interaction by integrating partial or subthreshold resonances using phased array enhancement operator resonance dynamics (step 224) with additional resonances synthetically induced to accommodate the possibility for the presence of single-point and two-point mutations around the mutation-centered pixels; and
- Resonance recombination (step 226).

[0037] A combination of one or more these enhancements are superimposed on the techniques described in the co-pending patent application to address specific sources of hybridization degradation, device imperfections and protocol variability in the analysis process to thereby enhance repeatability.

[0038] Referring now to FIG. 4, initially at step 300, a set of mutations of interest are selected and at step 301 preconditioner transforms are generated based upon the selected set of mutations. At step 302, Quantum Expressor Functions are generated based upon the Hamiltonian of a pre-selected basis system. Phase shifted resonance stimulus is generated, at step 304, using the Quantum Expressor functions. Grouping stimulus is also generated, at step 305.

[0039] Steps 300 - 305 are preferably performed off-line to set up the Quantum Expressor Functions and the corresponding resonance stimulus and grouping stimulus and need not be repeated other than to update the Quantum Expressor Functions to accommodate new and different DNA microarray patterns or if new mutations of interest need to be considered.

[0040] At step 306, a dot spectrogram is generated using a DNA microarray for which Quantum Expressor Functions have already been generated. At step 307, the dot spectrogram is tessellated to match morphological characteristics

of the Quantum Expressor Functions yielding a dot spectrogram tesselation (DST). At step **308**, local parametrics of the tessellated image are extracted. Then, at step **310**, an amount of amplitude wandering is determined and compared with pre-determined allowable generator function limits. If, at step **310**, the amplitude wandering is not within the allowable generator function limits, then execution proceeds to step **312** where the tessellated dot spectrogram to match spectral characteristics of the Quantum Expressor Functions. Steps **308** and **310** are repeated until the amplitude wandering is found to be within the pre-determined limits at which point execution proceeds to block **314** wherein a resonance interaction is performed between the tessellated, renormalized dot spectrogram and the phase shifted resonance stimulus generated at step **304** and the group stimulus generated at step **305** to identify any mutations represented by the dot spectrogram.

[0041] The actual resonant interaction, which involves convergent reverberations, includes the following sub-steps also shown in **FIG. 4**. At step **316**, a resonance dynamics iteration is initiated which includes the use of ensemble boundary and CSR operators **(step 318)** and the use of bulk property estimators **(step 320)**. The ensemble boundary filters, CSR filters and bulk property estimators are applied to the tessellated, re-normalized dot spectrogram in combination with the resonance and group stimulus. The resulting filtered dot spectrogram is then evaluated to determine a degree of resonance convergence to one or more of the set of predetermined mutations, at step **322**. The degree of convergence is evaluated, at step **324**, against a Lindbald condition and, if the Lindbald condition is not met, the system is deemed to be subject to paralysis of dynamics and execution proceeds to step **326** wherein possible hixel death is compensated for by increasing a time scale for the iteration initiated at step **316** and then repeating the iteration.

[0042] Here it should be noted that mutation death and paralysis of dynamics are different concepts. The mutation death check is a conditional check . If this check shows that a resonance is not possible for a specific mutation resonance centered (MRC)-hixel then the iteration is terminated and block **314** is exited. But failure of resonance dynamics is not sufficient to conclude that a specific mutation is absent. Indeed, if the "hixel death" check fails, that implies that resonance could be still obtained in a downstream iteration.

[0043] If, at step **324**, the iteration has converged and no paralysis has occurred, then one or more mutations have been reliably identified. Execution proceeds to block **325** wherein another resonant interaction is performed to identify particular diseases represented by the mutations. Briefly, at step **326**, a resonance dynamics iteration is initiated which includes the use of ensemble boundary and CSR operators **(step 328)** and the use of bulk property estimators **(step 330)**. The resulting filtered dot spectrogram is then evaluated to determine a degree of resonance convergence, at step **332**. The degree of convergence is evaluated, at step **334**, against a Lindbald condition and, if the Lindbald condition is not met, the system is deemed to be subject to paralysis of dynamics and execution proceeds to step **336** wherein a time scale for the iteration initiated at step **326** is increased before the iteration is repeated. If the Lindbald condition is met, then diseases corresponding to the mutations found using step **314** have been reliably identified.

[0044] Processing in accordance with step **335** depends on the biochip. The flowchart of **FIG. 4** illustrates a general form of the method requiring processing during step **335**. In other implementations, this step is trivial or can be eliminated entirely. In this regard, the overall method is implemented at two levels of abstraction, depending on how well the disease genomics is understood. Detection of a specific mutation is necessary and sufficient to conclude expression of a specific gene. But the expressed gene may not be the one to conclusively identify the disease. Then another level of abstraction is invoked wherein the method is applied inferentially by expanding the gene expression circuit or gene expression tree to determine if there is evidence that all expressed genes eventually lead to one that conclusively identifies the disease. So step **335** operates on the results of step **314**, such that all identified mutations are used as an input to determine if the complete expression pathway for leading up to the point that a disease can be concluded.

[0045] If the biochip is so designed that the mutations corresponding to all intermediate expressed products, from any disease starting point can be captured by resonance output of step **314**, then sub-steps within step **335** and subsequent steps **340** and **342** can be circumvented. If not, clustering step **340** and geometric hashing step **342** are provided to identify that an expression pathway is present that trivializes the disease conclusion =(**step 344**).

[0046] Once the diseases are identified, clustering properties are evaluated at step **340** to selectively eliminate oligonucleotides representing possible diagnoses based on morphological filtering of subthreshold resonances and any subsequent recentering (i.e. the inverse of dispersion). Steps **314 - 335** produce a cluster of sub-threshold resonances. Step **340** is a reverification such that all induced resonances are present in the target sample and not a manifestation of multiple rescalings and synthetic SNR enhancements.

[0047] Then a hashing projector is applied at step **342** to order the mutations. A diagnostic decision is then rendered at step **344** by examining the order of the mutations and comparing the mutations with a table identifying corresponding diseases.

[0048] Thus, the output of block **314** represents all hixels that identify complementary oligonucleotide bindings in the biological sample being analyzed and this represent "mutations". The output of block **335** comprises a set of expressed genes that are associated with a particular pathogenic pathway and thus represent a preliminary "diagnosis". Further analysis of the pathogenic pathway provides a set of possible diseases, if any. This decomposition is motivated by scaling the computation to answer three questions:

- Does the current condition imply predisposition to a specific disease?
- What is the likelihood of presence of a disease?
- What is the set of all possible diseases that may be concluded from the target sample, given a specific genomic encoding implemented by the biochip?

[0049] In any case, if the diagnostic decision rendered at step 344 is affirmative, then the diagnosis is output. If the diagnosis is negative then, at step 346, a determination is made as to whether there are any alternative mutations, not within the initial set of mutations selected at step 300, that could be present within the sample. This determination is made by examining a table listing all possible mutations. If there are alternative mutations, then the process is repeated from step 300. If not, then a signal is simply output indicating that no mutations were found in the sample.

[0050] Now details of the steps of the new method will be provided. Details regard steps already described in the co-pending application will not be repeated herein.

Mutations Sets

[0051] The mutation set of interest generated at step 300 is selected by identifying oligonucleotides representative of the {Z} mutations of interest. Each oligonucleotide is represented by $\psi(i,j)$ which is given by $[\alpha_0\alpha_1...\alpha_k]$, where α = {A,C,T,G} base associated with each array cell [a,b] where $10 \leq k \leq 25$. The entire set of unique oligonucleotides denoting mutations of interest, $\Delta(l,m)$, is given by $[\delta_0\delta_1...\delta_k]$ where δ = {A,C,T,G} length $|\Delta|$= length $|\psi|$, and $0 < ||\Delta - \psi|| \leq k$, and the designed in $\psi(l,m)$ oligonucleotide sequence is a perfect complement to only $\Delta(l,m)$ for all l,m.

[0052] As part of step 300, an oligonucleotide table is generated which contains the oligonucleotide sequences associated with each mutation of interest identified by row and column location (i,j). The oligonucleotide table is provided for subsequent use at step 312 to map locations within the dot spectrogram wherein resonance occurs at step 310 to oligonucleotides such that mutations present in a sample being analyzed are easily identified. Also as part of step 300, a mutation table is generated which contains the diseases associated with each mutation of interest. The mutation table is provided for subsequent use at step 314 to map mutations identified at step 312 to specific diseases or other medical conditions such that the diseases can be easily identified.

Basis System for Quantum Expressor Functions

[0053] The selection of the basis system and the generation of the QEF's based thereon depends, in part, and the characteristics of the DNA microarray. In the exemplary embodiment, the DNA microarray is an N by M DNA chip array wherein an element of the array is referred to herein as an "oxel": o(i,j).

[0054] The pre-hybridization microarray (PEBC) is expressed as:

$$PEBC = \sum_{1}^{N} \sum_{1}^{M} o(i,j),$$

where N and M refer to the linear (row and column) dimensions of the 2-D microarray.

[0055] The numeric value associated with each oxel is given by:

$$\hat{O}(i,j) = \alpha_k . 4^{k-1} + \alpha_{k-1} . 4^{k-2} + ... + \alpha_1 . 4^1 + \alpha_0 . 4^0$$

where $[\alpha] = [A|C|T|G]$ take the values $[0|1|2|3]$ respectively.

[0056] An element of the dot spectrogram is referred to herein as a hixel: h(i,j).

[0057] A spin boson basis system is selected for use with this type of array. Other basis system may be appropriate for either the same or other microarray configurations..

Quantum Expressor Functions

[0058] The QEF is generated at step 302 based upon the spin Boson basis system by first calculating the Hamiltonian for the system, calculating harmonic amplitudes $|P_m|$ for the Hamiltonian, generating an order function (OF), measuring entrainment entrainment states of the OF of the ground truth and finally modulating the OF of ground truth to yield the QEF.

[0059] The QEF's generated at step 302 are converted to a phase-space representation. Also, if the output of the

hybridization chip is not in phase space then it is converted as well. The conversion is performed using phase embedding operator, Γ, described in the co-pending application. Results associated with combinatorial Hopf Algebra are used to contain amplitude dispersion due to loss of hybridization. A special case of quantum random walk, Gelfand-Naimark Segal (GNS) construction is used to disperse group stimulus. Note that coproduct construct of the Hopf algebra plays the role of "sharing out" possible explanations of a fact. The GNS dispersion of QEF is implemented using an approximation:

$$\Phi_{QEF}(amp.vector) = \hat{U}_t a \hat{U}_t^{-1} \text{ where } \hat{U}_t = e^{-itH}$$

where H denotes the hamiltonian for the coupling spin boson system.

Generation and Tesselation of the Dot Spectrogram

[0060]   As noted a dot spectrogram is generated at step 306 for a sample from an N by M DNA chip array wherein an element of the array is an "oxel": $o(i,j)$. A 6-σ manufacturing process accuracy in microarray design is assumed. Each array cell amplitude is given by $\Phi(i,j)$ for i: 1 to N, and j: 1 to M. Let $\psi(i,j)$ denote the a priori known oligonucleotide given by $[\alpha_0\alpha_1...\alpha_k]$, where $\alpha = \{A,C,T,G\}$ base associated with each array cell [a,b] where $10 \leq k \leq 25$. The complimentary strand, derived from unknown sample is denoted by $\bar{\Psi}(i,j)$.

[0061]   The post-hybridization microarray is treated mathematically using the machinery of equations with aftereffect. Each hixel given by $\Phi(i,j)$ is represented as a cluster of dynamical systems of potentially [CB] correctly bound, [UB] unbound, [PB] partially bound and [IB] incorrectly bound. Thus $[CB]_{\Phi(i,j)} + [UB]_{\Phi(i,j)} + [PB]_{\Phi(i,j)} + [IB]_{\Phi(i,j)} = T_{\Phi(i,j)}$ within 0.0001%.

[0062]   The dot spectrogram $\Phi(i,j)$ is then tessellated to determine idealized ensemble boundaries for forcing downstream resonant action.

[0063]   Typically, in signal processing applications, high pass or band pass spatial filtering is implemented to enhance SNR in DS matrix. Alternate methods apply a combination of Laplacian or other edge detection filters apply to enhance signal from arrays cells with a higher hybridization concentration from those of the adjacent cells. These SNR enhancement methods however work only with positive or zero-SNR. Since SNR in general is negative in our case (ultra-low target DNA concentrations), these methods in effect amplify noise or further blur the hixel boundaries.

[0064]   Tesselation is performed by performing gradient refocusing and resealing as described in the co-pending application. In the alternative, a Dirichlet tessellation operator or a Delaunay triangulation operator are applied to tessellate the dot spectrogram.

Extraction of Local Parametrics and Calculation of Amplitude Wandering

[0065]   The tessellated image is treated as a metrically transitive random field. All properties associated with a singular (deterministic), homogeneous (i.e., stationary) field are subsumed.

[0066]   The parametric of most interest is the integrated density of states, given by

$$N(\lambda) = \lim_{L \to \infty} \frac{1}{\pi L} E\{\aleph(L)\}$$

where

$$\aleph' = \sqrt{\lambda} - \frac{q}{\sqrt{\lambda}} \sin^2 \aleph$$

whence

$$\aleph'\Big|_{\aleph = 0} = \sqrt{\lambda} > 0$$

where n is the number of eigenvalues to the system (random field approximation).

[0067] This is computed for each tessellation region in the dot spectrogram.

[0068] Amplitude wandering is determined using Palm generators as described in the co-pending patent #1. The Palm generators exploits the notion of generator functions to capture stochastic variability in hybridization binding efficacy. The exemplary method described herein draws upon results in stochastic integral geometry and geometric probability theory.

[0069] "Amplitude wandering estimate" that bounds the hixel amplitude dispersion due to total hybridization losses, is computed using Palm generators over the globally re-scaled dot spectrogram to capture amplitude wanderings and transitions at element, neighboring pair and local ensemble levels. Step 310 provides a measure for each mutation-recognizer centered (MRC-) hixel that is invariant to local degradation. The measure is expressed via the form

$$m(Z) = \int_Z f(z)dz$$

where Z denotes the set of mutations of interest. In other words, we determine the function f(z) under the condition that m(z) should be invariant with respect to all dispersions ξ. Also, up to a constant factor, this measure is the only one which is invariant under a group of motions in a plane. In principle, we derive deterministic analytical transformations on each MRC-hixel., that map error-elliptic dispersion bound defined on $\Re^2$ (the two dimension Euclidean space - i.e., oxel layout) onto measures defined on $\Re$. The dispersion bound is given by the form

$$Log_4(\hat{O}_{(i,j)}|^Z).$$

[0070] Recall that Palm distribution, Π of a translation (T_n) invariant, finite intensity point process in $\Re^n$ is defined to the conditional distribution of the process. It is expressed in terms of a Lebesgue factorization:

$$E_P N^* = \Lambda L_N \times \Pi$$

[0071] Where Π and Λ completely and uniquely determine the source distribution P of the translation invariant point process. The term $E_P N^*$ denotes the first moment measure of the point process and L_N is a probability measure. In patent #1 we described how to compute Π and A which can uniquely encode the dispersion and amplitude wandering associated with the MRC-hixel.

[0072] In this invention we relax the strong assumption that Palm generators, Π and Λ, capture all sources of stochasticity in dot spectrogram output. Since hybridization losses are affected in unknown and unpredictable ways, we need to modify the generators as probabilistic functions themselves. In other words the generators are converted to manifolds as opposed to a point function.

[0073] $(\rho_{m(i,j)}, \sigma_m, \eta_m, \varpi_m)$ specifies a continuous probability density function for amplitude wandering in the m-th MRC-hixel of interest where the terms denote:

oligonucleotide density per oxel $\rho_{m(i,j)}$, PCR amplification protocol (σ_m), fluorescence binding efficiency (η_m) and imaging performance (ϖ_m). Previously we required a preset binding dispersion limit to be apriori provided to compute Λ, given by the second moment to the function at SNR = 0.

[0074] Nondispersive Π is computed using $\Pi = \Theta * P$ where

$$P = \int_{\tau_1}^{\tau_2} \wp(\rho_{m(i,j)}, \sigma_m, \eta_m, \varpi_m)\partial\tau$$

[0075] And τ_1 and τ_2 represent normalized hybridization dispersion limits (typically preset to 0.1 and 0.7 respectively to assume losses between 10% - 70% hybridization.

[0076] Preconditioned dot spectrogram is represented by $\hat{\Phi}(i,j)$. where function $1/(1+exp(\wp(...)))$ was used to express the underlying known and stationary point process.

[0077] The latter assumption is relaxed in this method and determination of whether the amplitude wandering is within allowable generator function limits is achieved by:

$$\frac{\Pi_0 - |\xi|^2}{\xi_1 \xi_2 ... \xi_k} \leq \Pi_0 \leq \frac{\Pi_0 + |\xi|^2}{\xi_1 \xi_2 ... \xi_k}$$

where

Π_0 denotes the nondispersive generator.

$\xi_1, \xi_2, ..., \xi_k$ provide the Laplace characteristic functional of the Poisson random field associated with each source of hybridization degradation. The contributions are estimated using

$$\sqrt{\xi_i} = c_d \cdot (det \hat{a}_i)^{-\frac{1}{2}} \lambda_0^{d/2}$$

where c is gain constant and $\hat{a}$ denotes a nonrandom matrix

$$\hat{a} = \{\hat{a}_{ij} : 1 \leq i, j \leq d\}$$

given by

$\hat{a}_{ij} = E\{a_{ik}(\xi) \psi_{kj}(\xi)\}$ and are metrically transitive fields representing the unique solution of the following variational problems:

$$E\{\psi_{li}(\xi) a_{lk} \ \psi_{kj}(\xi)\} \rightarrow \infty \tag{i}$$

$$rot\psi_i = \frac{\partial \psi_{ij}}{\psi_k} - \frac{\partial \psi_{ki}}{\psi_j} = 0 \tag{ii}$$

$$E\{\psi_{ji}(\xi)\} = \delta_{ji} \tag{iii}$$

$$E\{\psi_{ji}(\xi)\psi_{ji}(\xi)\} < \infty \tag{iv}$$

[0078] The differential operator for the metrically transitive field for convoling the uncertainty parameters is denoted by A_0. Population and solution of the above equation requires estimates for the forward sensitivity matrix of variables impacting hybridization degradation.

[0079] Renormalization at step 312, if necessary, is performed on the tessellated image to further match spectral properties of the stimulus pattern The re-normalization of the dot spectrogram is achieved by resealing the dot spectrogram in the interval [-π, +π]. The entire calculation proceeds in the phase space which is why we transformed the system to the metrically transitive random field.

Resonant Interaction to Identify Mutations

[0080] As noted, at step 314, the resonant interaction between the QEF and the tessellated, re-normalized dot spectrogram is performed until a pre-selected degree of convergence is achieved. Resonance dynamics relaxation values are calculated at step 316 as follows.

[0081] A closed-form convolutionless evolution equation is given by:

$$\underset{DST_i}{\varphi}(t) = \Theta(t, \tau) \underset{DST_i}{\varphi}(\tau)$$

where

$$\frac{\partial \Theta(t,\tau)}{\partial t} = \underset{DST}{\psi}(t,\tau) \underset{DST_i}{\varphi}(t,\tau)$$

where both depend upon the normalized DST_I (i.e., initial state) at time τ - post-hybridization but pre-conditioned state. And $\underset{\infty}{\psi'}(t,\tau)$ is the unitary evoluter $e^{-i(t-\tau)\tilde{H}}$

for the hamiltonian specifying the after affect basis system dynamics.

[0082] Also,

$$\underset{DST_i}{\varphi}(t,\tau) = \lim_{\varepsilon \to 0} \frac{1}{\varepsilon} \left[\underset{DST}{\psi}(t+\varepsilon,\tau) - 1 \right]$$

[0083] In practice a small ε, typically 10^{-6} is used.

[0084] So if theoretical convergence time is τ_0 (outer convergence cycle time) and choosing $t > \tau + \tau_0$, then:

$$\underset{DST_i}{\varphi}(t) = \Theta(t,\tau + \tau_0) \underset{DST_i}{\varphi}(\tau + \tau_0)$$

and

$$\Theta(t,\tau') = \lambda \left[\int_t^t \varphi(t')dt' \right]$$

and λ is a time-ordering operator.

[0085] The dynamics relaxation values are then filtered at step 318 using ensemble boundary and CSR filters (higher order Poisson kernel) as follows:

$$\underset{DST_i}{\varphi}(t) * e^{-P(|\Theta|)}$$

where

$$P_r(|\Theta|) = \frac{1-r^2}{1-2r\text{Cos}+r^2}$$

where $r \geq 0$.

[0086] The bulk property estimators of step 320 are applied to the dynamics relaxation values as follows:

$$\frac{1}{2\pi} \int_{DST_i} P_r(t-|\Theta|)dt$$

where t is the discretization step.

[0087] The above expression provides an estimate of when a geomteric motion embodied by the convolutionless equation, is no longer a plausible resonance candidate.

[0088] This is the closed form for an expression at which the coupling between DST and the microarray is broken

and a coupling with a nonlinear information filter (NIF) is established. In essence, the system forgets any initial correlation and tends to a Lindbald condition.

[0089] The resonance convergence is determined at step **322** as follows:

$$\text{Log } \frac{|U(t+1)-U_{\lambda[AVG]}|}{|U(t)-U_{\lambda[AVG]}|} \geq 1$$

[0090] The system oscillates if no convergence is reached. If increasing the timescale x-times (~5) does not meet the condition, then the mutation is deemed to be absent.

[0091] It should be noted that, unlike the technique of the co-pending application, in the present invention the absence of resonance over a maximum interation count does not imply absence of resonance. The reason is that both the dot spectrogram and the QEF are dispersed, i.e., the SNR is reduced over an individual hixel, but is in fact increased over an ensemble. So the convergence decisions are made by cascading the inner loop reverberations as opposed to a single reverberation. So two timecycles are used for the convergence analysis:

(a) time cycle over which hyperfine resonances are tracked, detected and used as a decision mechanisms to continue or stop the interation;
(b) time cycle over which the absense of mutation is actually concluded. This is done by implementing a local maxima over output of previous step and then reintegrating.The method essentially accumulates partial resonances and then applies the same resonance equation to the reseated and renormalized partial stage.

[0092] This process can be analytically be represented as:

$$(\tau_1,\tau_2) = \sum_{DST} c_3(\tau_2)\left[\oint c_2(\tau_2) \otimes \left[\frac{1}{C(\tau_2)}\left[\sum_{DST} c_1(\tau_2) \otimes \oint_{DST_i} U_{\lambda[AVG]}d\tau_1 \right] > 0 \atop 0 \quad\quad\quad\quad\quad otherwise \right] \right]d\tau_2$$

where c_1, c_2 and c_3 are thresholding constants that are used to detect subthreshold resonances. Also, $c_1 \gg c_2 \gg c_3 \gg$ l/[amplitude resolution].

[0093] Also τ_1 and τ_2 refer to the inner and outer integration timescales. In an implementation they refer to the iteration conter at which the integration loop is terminated, exceeded or exited. Typically termination counter is set to one thousand steps with timescale of the order of ten nanoseconds for inner step and microsecond for outer step. So effective device convergence time is within onen hundred milliseconds for the entire computation.

[0094] In this regard, if the Lindbald condition is not achieved and verified the dynamics is considered paralyzed.

[0095] The paralysis of dynamics actually implies that coupling between

(a) the Quantum Expressor Function,
(b) the tessellated and normalized dot spectrogram , and
(c) the convolutionless carrier

is too weak to exhibit a nonlinear resonance. The physical interpretation is that the coupled system exhibits "frustrated dynamics" which enhances and impedes resonance reaction at the same time. So the actual output takes the form of white noise over several hixels which oscillates.

[0096] The detection of oscillation occurs when the spectral radius for the convergence criteria oscillates between limits $[\varepsilon_1, \varepsilon_2]$ and does not tend towards 0.This may be verified by tracking the spectral radius zero crossing with respect to the lower bound ε_1. If the zero crossing frequency exceeds a present number (e.g., 10) in this implementation, the dynamics is deemed paralyzed.

If a paralysis of dynamics has occurred, a "mutation death" is evaluated as follows. The check for MRC hixel death relates to the verification of a suprathreshold resonance, where the resonance is defined as the integrand of partial resonances over the entire DST structure, i.e,

$$(r_1 r_2) = \sum_{DST} c_3(r_2) \left[\oint c_2(r_2) \otimes \left[\frac{1}{C(r_2)} \left[\begin{array}{cc} \sum_{DST} c_1(r_2) \otimes \oint_{DST} U_{\int_{\Lambda[AVG]} dr_1} & > & 0 \\ 0 & & otherwise \end{array} \right] \right] dr_2 \right]$$

$$> K$$

$\forall \; \tau_1, \tau_2 \leq$ predefined upper limit. Typically set to 100 for outer iteration and 1000 for inner iterations.

[0097] The time scale for realization of the Lindbald condition is changed and the system reiterated.

[0098] Hence the final output of step **314** is all hixels that identify complementary oligonucleotide bindings in the biological sample which are represented computationally by the set $\{h_k(i,j)\}$ where $\{h_k(i,j)\}$ is the corresponding oligonucleotide sequence $[\alpha_0 \alpha_1 ... \alpha_k]$ for the kth surviving hixel.

Resonant Interaction to Identify Diseases

[0099] The mutations identified using block **314** are processed using similar steps within block **325** to identify diseases represented by the mutations. Hence the final output of step **335** is a set of expressed genes that are associated with a particular pathogenic pathway which is represented computationally by the set $\{\psi^l_k(i,j)\}$ where $\{\psi^l_k(i,j)\}$: $[\alpha_0 \alpha_1 ... \alpha_k]$ for the l-th element of the pathway capturing the k-th disease.

[0100] For single disease analysis steps **324** - **334**, i.e., block **335** can be omitted.

Clustering Property Check

[0101] Diseases identified using block **325** are processed at step **340** to identify clustering properties as follows. The clustering operation is essentially a pruning operation based on morphological filtering of subthreshold resonances and subsequent recentering(i.e. the inverse of dispersion).

[0102] The clustering computation is based on transversal ordering (is based on transversal numbers) of the oligonucleotide sequencing underlying the resonance-centers for all subthreshold resonances. The concept draws from a result in hypergraph theory. Recall that transversal of a hypergraph $H = \{X: E_1, E_2, ..., E_m)$ is defined to be a set $T \subset X$ such that $T \cap E_i \neq \phi$ for $l = 1, 2, ..., m$, where $E_1, E_2, .., E_M$ define subgraphs.

[0103] In this method, each oligonucleotide, associated with a mutation that survives "hixel-death" during resonant reverberation iterations, is represented by $\psi(i,j)$: $[\alpha_0 \alpha_1 ... \alpha_k]$, where $\alpha = \{A,C,T,G\}$ base associated is treated as a subgraph of the total set of unknown mutations that are actually present in the target sample. If the surviving hixel is an ensemble than each ensemble is treated as a subgraph with multiple nodes and several edges. If only an individual hixel survives than it is treated as a single node subgraph. Transversal number of a hypergraph, H, is defined as the minimum number of vertices in a transversal. It is given by :

$$\bar{\tau}(H) \;\; = \;\; \min|T|$$

[0104] The sub-steps involved in clustering are:

- determine $Min \Im = \{A_1, A_2, ..., A_k\}$. where A_1, A_2, .., A_k denote the surviving resonance clusters.
- Next determine the following families:

$$\Im_1 = \{A_1\} \quad \rightarrow \quad Tr\{A_1\} = (\{a\}/a \in A_1)$$

$$\Im_2 = \Im_1 \cup \{A_2\} \quad \rightarrow \quad Tr\{\Im_2\} = Min(Tr \, \Im_1 \vee Tr\{A_2\})$$

$$\Im_3 = \Im_2 \cup \{A_3\} \quad \rightarrow \quad Tr\{\Im_3\} = Min(Tr \, \Im_2 \vee Tr\{A_3\})$$

$$\mathfrak{I}_4 = \dots$$

5   If Min A has k members, then the algorithm constructs Tr A = Tr ϑ_k in k steps.

Hashing Projector

[0105]   A hashing projector is then applied at step **342** to the output of the clustering check. The hashing projector
10   produces an enumeration of the leading k oligonucleotides with the highest transveral numbers. So a set of mutations
or the corresponding expressed genes are created that have the highest sorted transversal numbers. Typically, all
members that are seperated by a distance of, at most two, are chosen.

Diagnostic Decision
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[0106]   A diagnostic decision is rendered at step **344** based upon the output of the hashing projector. The diagnostic
decision is achieved using a simple table lookup that is indexed by the results of hashing projection computation using
the aforementioned tables.

20   Alternatives

[0107]   Alternative possible mutations are evaluated at step **346**.
If alternatives are available, the alternative set of mutations of interest are loaded and the process is repeated beginning
at step **300**. Hence, if the original set of mutations from which the original set of QIF's were generated during the off-
25   line process of steps **301** and **302**, did not include the alternative mutations, then the off-line process is repeated with
the new set of mutations to generate new QIF's.
[0108]   In the event that method yields (and it often does) multiple disease detection hypotheses, all possible hypoth-
eses are provided as plausible candidates.
[0109]   The technique described with respect to **FIG. 4** is particularly powerful in that it provides an enumerative
30   solution which generally covers all possible diagnostic candidates as opposed to only one or two, given the best ge-
nomic understanding or mapping between expressed genes and diseases.

Alternative Embodiments

35   [0110]   Details regarding an implementation directed to measuring viral loads may be found in U.S. Patent 6,245,511,
entitled "Exponentially Convergent Therapy Effectiveness Monitoring Using Viral Load Measurements".
[0111]   The exemplary embodiments have been primarily described with reference to flow charts illustrating pertinent
features of the embodiments. Each method step also represents a hardware or software component for performing the
corresponding step. These components are also referred to herein as a "means for" performing the step. It should be
40   appreciated that not all components of a complete implementation of a practical system are necessarily illustrated or
described in detail. Rather, only those components necessary for a thorough understanding of the invention have been
illustrated and described in detail. Actual implementations may contain more components or, depending upon the
implementation, may contain fewer components.

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Claims

1. A method for analyzing an output pattern of an arrayed microdevice to identify mutations, if any, present in a
biological sample applied to the arrayed microdevice, said method comprising the steps of:
50

        tessellating the output pattern;
        generating a stimulus pattern associated with the set of known mutations;
        generating a resonance pattern representative of resonances between the stimulus pattern and the tessellated
        output pattern;
55   interpreting the resonance pattern to yield a set of confirmed mutations by comparing resonances found therein
        with predetermined resonances expected for the selected set of mutations.

2. The method of claim 1 wherein the output pattern is derived from an arrayed microdevice having a plurality of cells

each having a set of substantially identical immobilized oligonucleotides with the oligonucleotides of each cell being substantially unique from the oligonucleotides of every other cell.

3. The method of claim 1 wherein said step of tessellating the output pattern comprises the step of amplifying highly local morphological variations in the output pattern.

4. The method of claim 3 wherein the stimulus pattern is generated based upon Quantum Expressor Functions and wherein said step of tessellating the output pattern is performed to tessellate the output pattern to match morphological characteristics of the Quantum Expressor Functions.

5. The method of claim 1 further including the steps of:

   extracting local parametrics from the tessellated output pattern;
   determining whether a degree of amplitude wandering representative of the local parametrics is within a predetermined allowable generator function limit; and
   if not, renormalizing the tessellated output pattern to further match spectral properties of the resonance pattern.

6. The method of claim 5 wherein said step of extracting local parametrics from the tessellated output pattern comprises the steps of
   extracting parameters representative of an integrated density of states within each of a plurality of tesselation regions within the tessellated output pattern.

7. The method of claim 5 wherein a degree of amplitude wandering is determined by applying a Palm distribution to develop generators for estimating stochastic wandering.

8. The method of claim 1 further including the step of transforming the tessellated output pattern and the stimulus pattern to a metrically transitive random field.

9. The method of claim 8 further including the step of renormalizing the tessellated output pattern following transformation to the metrically transitive random field.

10. The method of claim 9 wherein said step of renormalizing is performed to rescale the tessellated output pattern to the interval $[-\pi, +\pi]$.

11. The method of claim 1 wherein the step of generating a stimulus pattern associated with the set of known mutations comprises the steps of:

   selecting a sub-set of the mutations for analysis; and
   selecting a sub-set of nonlinear Quantum Expressor Functions from a set of predetermined nonlinear Quantum Expressor Functions based upon the selected sub-set of mutations.

12. The method of claim 11 further including the steps of:

   transforming the nonlinear Quantum Expressor Functions and the tessellated output pattern into phase space.

13. The method of claim 1 wherein the step of generating a resonance pattern includes the step of
   iteratively processing the output pattern by performing a convergent reverberation to yield a resonance pattern representative of resonances between a predetermined set of selected Quantum Expressor Functions and the tessellated output pattern until a predetermined degree of convergence is achieved between the resonances found in the resonance pattern and resonances expected for the set of mutations.

14. The method of claim 13 wherein the step of iteratively processing the output pattern by performing a convergent reverberation includes the step of performing a convergent reverberant dynamics resonance analysis of the tessellated output pattern using the resonance stimulus pattern to identify mutations represented by the tessellated output pattern.

15. The method of claim 14 wherein the step of performing a convergent reverberant dynamics resonance analysis includes the steps of: .

a) determining a first set of resonance dynamics relaxation values based upon the preconditioned output pattern and the resonance stimulus;

b) filtering the dynamics relaxation values using ensemble boundary and CSR filters to yield a second set of values;

c) applying bulk property estimators to the dynamics relaxation values to yield a third set of values;

d) evaluating the second and third sets of values to determine a degree of resonance convergence; and

e) determining from the degree of resonance convergence whether a paralysis of dynamics has occurred and, if so, repeating steps a) - e).

16. The method of claim 15 wherein said step of determining resonance dynamics relaxation values based upon the preconditioned output pattern and the resonance stimulus comprises the steps of
applying a convolutionless evolution operator to the tessellated output pattern.

17. The method of claim 15 wherein said step of applying bulk property estimators to the dynamics relaxation values to yield a third set of values comprises the steps of
applying a coupling operator to which couples the dynamics relaxation values representative of the tessellated output pattern to a nonlinear information filter.

18. The method of claim 15 wherein said step of evaluating the second and third sets of values to determine a degree of resonance convergence comprises the steps of
determining whether the third set of values oscillate beyond and predetermined threshold after a predetermined period of time and, if not, convergence has been achieved.

19. The method of claim 18 wherein if no convergence has been achieved, performing the additional step of increasing a timescale for determining convergence beyond the predetermined period of time and, if convergence is still not achieved, then generating a signal indicating that none of the mutations of the mutation set are present in the sample.

20. The method of claim 15 wherein said step of determining whether a paralysis of dynamics as occurred comprises the steps of evaluating a Lindbald condition and, if the Lindbald condition has not been achieved generating a signal indicating that paralysis of dynamics has occurred.

21. The method of claim 20 wherein, if a paralysis of dynamics has occurred, performing the additional steps of determining whether a "mutation death" has occurred by varying a time scale for realization of the Lindbald condition and repeating the steps beginning with determining resonance dynamics relaxation values.

22. The method of claim 13 wherein the step of iteratively processing the output pattern by performing a convergent reverberation also includes the step of performing a convergent reverberant dynamics resonance analysis of the mutations using the resonance stimulus pattern to identify diagnostic conditions represented by the mutations.

23. The method of claim 22 wherein the step of performing a convergent reverberant dynamics resonance analysis of the mutations using the resonance stimulus pattern to identify diagnostic conditions represented by the mutations includes the steps of:

a) determining resonance dynamics relaxation values based upon the resonance stimulus and the mutations;

b) filtering the dynamics relaxation values using ensemble boundary and CSR filters to yield a second set of values;

c) applying bulk property estimators to the dynamics relaxation values to yield a third set of values;

d) evaluating the second and third sets of values to determine whether a predetermined degree of resonance convergence has been achieved; and

e) if no convergence, repeat steps a) - e).

24. The method of claim 1 further including the step of filtering the diagnostic conditions identified by the convergent reverberant dynamics resonance analysis based upon clustering properties.

25. The method of claim 1 wherein the biological sample is selected from a group consisting of a DNA, RNA, protein, peptide-nucleic acid (PNA) and targeted nucleic amplification (TNA) samples.

26. The method of claim 1 further including the step of rendering a diagnostic decision based on the diagnotic conditions identified by the convergent reverberant dynamics resonance analysis.

27. The method of claim 26 wherein
> if said diagnostic decision is negative, then determining whether any alternatives are available; and
> if no alternatives are available, selecting a new sub-set of mutations and repeating all steps.

28. A system for analyzing an output pattern of an arrayed microdevice to identify mutations, if any, present in a biological sample applied to the arrayed microdevice, said system comprising:

> a tesselation unit operative to tessellate the output pattern;
> a stimulus pattern generation unit operative to generate a stimulus pattern associated with the set of known mutations;
> a resonance pattern generation unit operative to generate a resonance pattern representative of resonances between the stimulus pattern and the tessellated output pattern;
> a resonance pattern interpretation unit operative to interpret the resonance pattern to yield a set of confirmed mutations by comparing resonances found therein with predetermined resonances expected for the selected set of mutations.

29. The system of claim 28, further comprising:

> an extraction unit operative to extract local parametrics from the tessellated output pattern;
> a determination unit operative to determine whether a degree of amplitude wandering representative of the local parametrics is within a predetermined allowable generator function limit; and
> a renormalization unit operative to renormalize the tessellated output pattern to further match spectral properties of the resonance pattern if the determination unit determines that the degree of amplitude wandering is not within the predetermined allowable generator function limit.

30. The system of claim 28 for performing a convergent reverberant dynamics resonance analysis of the output pattern to identify the mutations represented thereby, further comprising:

> a determination unit operative to determine a first set of resonance dynamics relaxation values based upon the tessellated output pattern and the resonance stimulus;
> a filter operative to filter the dynamics relaxation values using ensemble boundary and CSR filters to yield a second set of values;
> an estimator unit operative to apply bulk property estimators to the dynamics relaxation values to yield a third set of values;
> an evaluation unit operative to evaluate the second and third sets of values to determine whether a predetermined degree of resonance convergence has been achieved; and
> a paralysis detection unit operative to detect whether a paralysis of dynamics has occurred.

31. The system according to claim 28, wherein said stimulus generation unit generates stimulus pattern based on Quantum Expressor Functions.

32. The method according to one of the claims 1 to 27 wherein an output pattern of a biochip is used as the arrayed microdevice output pattern.

33. The system according to one of the claims 28 to 31 for analyzing an output pattern of a biochip as the arrayed microdevice output pattern.

Patentansprüche

1. Verfahren zum Analysieren eines Ausgabemusters einer Mikroarrayvorrichtung, um in einer auf die Mikroarrayvorrichtung aufgebrachten biologischen Probe, wenn überhaupt, vorhandene Mutationen zu identifizieren, wobei das Verfahren die Schritte umfasst:

> Tessellieren des Ausgabemusters,

Erzeugen eines der Gruppe bekannter Mutationen zugeordneten Stimulusmusters,

Erzeugen eines Resonanzmusters, das Resonanzen zwischen dem Stimulusmuster und dem tessellierten Ausgabemuster angibt,

Interpretieren des Resonanzmusters, um eine Gruppe bestätigter Mutationen zu erhalten, indem darin aufgefundene Resonanzen mit für die Gruppe von Mutationen erwarteten, vorbestimmen Resonanzen verglichen werden.

2. Verfahren nach Anspruch 1, bei dem das Ausgabemuster von einer Mikroarrayvorrichtung erhalten wird, die eine Mehrzahl Zellen aufweist, die jeweils eine Gruppe im Wesentlichen identischer, immobilisierter Olionukleotide aufweisen, wobei die Olionukleotide jeder Zelle gegenüber den Olionukleotiden jeder anderen Zelle im Wesentlichen eindeutig sind.

3. Verfahren nach Anspruch 1, bei dem der Schritt, das Ausgabemuster zu tessellieren, den Schritt umfasst, lokale morphologische Variationen im Ausgabemuster stark zu verstärken.

4. Verfahren nach Anspruch 3, bei dem das Stimulusmuster basierend auf Quantum-Expressor-Funktionen erzeugt wird, und bei dem der Schritt, das Ausgabemuster zu tessellieren, durchgeführt wird, um das Ausgabemuster so zu tessellieren, dass es morphologischen Charakteristika der Quantum-Expressor-Funktionen entspricht.

5. Verfahren nach Anspruch 1, ferner die Schritte umfassend:

Extrahieren lokaler Parameter aus dem tessellierten Ausgabemuster,
Bestimmen, ob ein Ausmaß einer die lokalen Parameter angebenden Amplitudenwanderung innerhalb eines vorbestimmten, zulässigen Generatorfunktionsgrenzwerts liegt, und
wenn dies nicht der Fall ist, Renormalisieren des tessellierten Ausgabemusters, um ferner mit spektralen Eigenschaften des Resonanzmusters übereinzustimmen.

6. Verfahren nach Anspruch 5, bei dem der Schritt, lokale Parameter aus dem tessellierten Ausgabemuster zu extrahieren, die Schritte umfasst,
Extrahieren von Parametern, die eine integrierte Dichte von Zuständen in jedem einer Mehrzahl von Tessellierungsbereichen in dem tessellierten Ausgabemuster angeben.

7. Verfahren nach Anspruch 5, bei dem das Ausmaß der Amplitudenwanderung bestimmt wird, indem eine Palm-Verteilung angewendet wird, um Generatoren zum Abschätzen einer stochastischen Wanderung zu entwickeln.

8. Verfahren nach Anspruch 1, ferner den Schritt umfassend, das tessellierte Ausgabemuster und das Stimulusmuster in ein metrisch transitives Zufallsfeld umzuwandeln.

9. Verfahren nach Anspruch 8, ferner den Schritt umfassend, das tessellierte Ausgabemuster nach einer Umwandlung in das metrisch transitive Zufallsfeld zu renormalisieren.

10. Verfahren nach Anspruch 9, bei dem der Renormalisierungsschritt durchgeführt wird, um das tessellierte Ausgabemuster auf das Intervall $[-\pi, +\pi]$ zu reskalieren.

11. Verfahren nach Anspruch 1, bei dem der Schritt, ein der Gruppe bekannter Mutationen zugeordnetes Stimulusmuster zu erzeugen, die Schritte umfasst:

Auswählen einer Untergruppe der Mutationen zur Analyse, und
Auswählen einer Untergruppe nicht linearer Quantum-Expressor-Funktionen aus einer Gruppe vorbestimmter, nicht linearer Quantum-Expressor-Funktionen basierend auf der ausgewählten Untergruppe von Mutationen.

12. Verfahren nach Anspruch 11, ferner die Schritte umfassend:

Transformieren der nicht linearen Quantum-Expressor-Funktionen und des tessellierten Ausgabemusters in den Phasenraum.

13. Verfahren nach Anspruch 1, bei dem der Schritt, ein Resonanzmuster zu erzeugen, den Schritt umfasst
iteratives Verarbeiten des Ausgabemusters, indem ein konvergentes Nachhallen durchgeführt wird, um ein

Resonanzmuster zu erhalten, das Resonanzen zwischen einer vorgestimmten Gruppe ausgewählter Quantum-Expresser-Funktionen und dem tessellierten Ausgabemuster angibt, bis ein vorbestimmter Konvergenzgrad zwischen den in dem Resonanzmuster aufgefundenen Resonanzen und für die Gruppe von Mutationen erwarteten Resonanzen erreicht wird.

14. Verfahren nach Anspruch 13, bei dem der Schritt, das Ausgabemuster iterativ zu verarbeiten, indem ein konvergentes Nachhallen durchgeführt wird, den Schritt umfasst, eine Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen des tessellierten Ausgabemuters durchzuführen, wobei das Resonanzstimulusmuster verwendet wird, um von dem tessellierten Ausgabemuster angegebene Mutationen zu identifizieren.

15. Verfahren nach Anspruch 14, bei dem der Schritt, eine Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen durchzuführen, die Schritte umfasst:

a) Ermitteln einer ersten Gruppe von Resonanzdynamikrelaxationswerten basierend auf dem vorverarbeiteten Ausgabemuster und dem Resonanzstimulus,
b) Filtern der Dynamikrelaxationswerte unter Verwendung von Ensemblegrenz- und CSR-Filtern, um eine zweite Gruppe von Werten zu erhalten,
c) Anwenden von Masseeigenschaftsschätzfunktionen auf die Dynamikrelaxationswerte, um eine dritte Gruppe von Werten zu erhalten,
d) Evaluieren der zweiten und dritten Gruppe von Werten, um einen Resonanzkonvergenzgrad zu ermitteln, und
e) Ermitteln aus dem Resonanzkonvergenzgrad, ob eine Dynamiksperrung aufgetreten ist, und, wenn dies der Fall ist, wiederholen der Schritte a) - e).

16. Verfahren nach Anspruch 15, bei dem der Schritt, basierend auf dem vorverarbeiteten Ausgabemuster und dem Resonanzstimulus Resonanzdynamikrelaxationswerte zu bestimmen, die Schritte umfasst
Anwenden eines faltungslosen Entwicklungsoperators auf das tessellierte Ausgabemuster.

17. Verfahren nach Anspruch 15, bei dem der Schritt, Masseeigenschaftsschätzfunktionen auf die Dynamikrelaxationswerte anzuwenden, um eine dritte Gruppe von Werten zu erhalten, die Schritte umfasst
Anwenden eines Kopplungsoperators, mit dem die das tessellierte Ausgabemuster angebenden Dynamikrelaxationswerte gekoppelt sind, auf einen nicht linearen Informationsfilter.

18. Verfahren nach Anspruch 15, bei dem der Schritt, die zweiten und dritten Gruppen von Werten zu evaluieren, um einen Resonanzkonvergenzgrad zu ermitteln, die Schritte umfasst
Ermitteln, ob die dritte Gruppe von Werten nach einer vorbestimmten Zeitdauer über einen vorbestimmten Grenzwert hinaus oszillieren und, falls dies nicht der Fall ist, Konvergenz erreicht wurde.

19. Verfahren nach Anspruch 18, bei dem, wenn keine Konvergenz erreicht wurde, der zusätzliche Schritt durchgeführt wird, einen Zeitmaßstab zu vergrößern, um nach der vorbestimmten Zeitdauer Konvergenz festzustellen, und, wenn Konvergenz weiterhin nicht erreicht wird, dann ein Signal zu erzeugen, das angibt, dass keine Mutationen der Mutationsgruppe in der Probe vorliegen.

20. Verfahren nach Anspruch 15, bei dem der Schritt, zu ermitteln, ob eine Dynamiksperrung aufgetreten ist, die Schritte umfasst, eine Lindbald-Bedingung zu evaluieren, und, wenn die Lindbald-Bedingung nicht erreicht wurde, ein Signal zu erzeugen, das angibt, dass eine Dynamiksperrung aufgetreten ist.

21. Verfahren nach Anspruch 20, bei dem, wenn eine Dynamiksperrung aufgetreten ist, die zusätzlichen Schritte ausgeführt werden, festzustellen, ob ein "Mutationstod" aufgetreten ist, indem ein Zeitmaßstab zur Realisierung der Lindbald-Bedingung variiert und die Schritte beginnend mit der Ermittlung von Dynamikresonanzrelaxationswerten wiederholt werden.

22. Verfahren nach Anspruch 13, bei dem der Schritt, das Ausgabemuster iterativ zu verarbeiten, indem ein konvergentes Nachhallen durchgeführt wird, auch den Schritt umfasst, eine Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen der Mutationen durchzuführen, wobei das Resonanzstimulusmuster verwendet wird, um von den Mutationen angegebene, diagnostische Zustände zu identifizieren.

23. Verfahren nach Anspruch 22, bei dem der Schritt, eine Analyse hinsichtlich konvergenter Nachhalldynamikreso-

nanzen der Mutationen unter Verwendung des Resonanzstimulusmusters durchzuführen, um von den Mutationen angegebene, diagnostische Zustände zu identifizieren, die Schritte umfasst:

a) Ermitteln einer ersten Gruppe von Resonanzdynamikrelaxationswerten basierend auf dem Resonanzstimulus und den Mutationen,
b) Filtern der Dynamikrelaxationswerte unter Verwendung von Ensemblegrenz- und CSR-Filtern, um eine zweite Gruppe von Werten zu erhalten,
c) Anwenden von Masseeigenschaftsschätzfunktionen auf die Dynamikrelaxationswerte, um eine dritte Gruppe von Werten zu erhalten,
d) Evaluieren der zweiten und dritten Gruppe von Werten, um einen Resonanzkonvergenzgrad zu ermitteln, und
e) Ermitteln aus dem Resonanzkonvergenzgrad, ob eine Dynamiksperrung aufgetreten ist, und, wenn dies der Fall ist, wiederholen der Schritte a) - e).

24. Verfahren nach Anspruch 1, ferner den Schritt umfassend, die durch die Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen identifizierten diagnostischen Zustände basierend auf Clustereigenschaften zu filtern.

25. Verfahren nach Anspruch 1, bei dem die biologische Probe aus einer Gruppe ausgewählt ist, die aus DNA-, RNA-, Protein-, Peptid-Nucleinsäure-(PNA)- und Zielzellkernverstärkungs-(TNA)-Proben besteht.

26. Verfahren nach Anspruch 1, ferner den Schritt umfassend, basierend auf den durch die Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen identifizierten, diagnostischen Zuständen eine diagnostische Entscheidung zu treffen.

27. Verfahren nach Anspruch 26, bei dem
    wenn die diagnostische Entscheidung negativ ist, dann ermittelt wird, ob irgendwelche Alternativen verfügbar sind, und
    wenn keine Alternativen verfügbar sind, eine neue Untergruppe von Mutationen ausgewählt und alle Schritte wiederholt werden.

28. System zum Analysieren eines Ausgabemusters einer Mikroarrayvorrichtung, um in einer auf die Mikroarrayvorrichtung aufgebrachten biologischen Probe, wenn überhaupt, vorhandene Mutationen zu identifizieren, wobei das System umfasst:

    eine Tessellierungseinheit, die betriebsfähig ist, das Ausgabemuster zu tessellieren,
    eine Stimulusmustererzeugungseinheit, die betriebsfähig ist, ein Stimulusmuster zu erzeugen, das der Gruppe bekannter Mutationen zugeordnet ist,
    eine Resonanzmustererzeugungseinheit, die betriebsfähig ist, ein Resonanzmuster zu erzeugen, das Resonanzen zwischen dem Stimulusmuster und dem tessellierten Ausgabemuster angibt,
    eine Resonanzmusterinterpretationseinheit, die betriebsfähig ist, das Resonanzmuster zu interpretieren, um eine Gruppe bestätigter Mutationen zu erhalten, indem darin aufgefundene Resonanzen mit für die Gruppe von Mutationen erwarteten, vorbestimmten Resonanzen verglichen werden.

29. System nach Anspruch 28, ferner umfassend:

    eine Extraktionseinheit, die betriebsfähig ist, lokale Parameter aus dem tessellierten Ausgabemuster zu extrahieren,
    eine Ermittlungseinheit, die betriebsfähig ist, zu ermitteln, ob ein Ausmaß einer die lokalen Parameter angebenden Amplitudenwanderung in einem vorbestimmten, zulässigen Generatorfunktionsgrenzwert liegt, und
    eine Renormalisierungseinheit, die betriebsfähig ist, das tessellierte Ausgabemuster zu renormalisieren, um ferner mit spektralen Eigenschaften des Resonanzmusters übereinzustimmen, wenn die Ermittlungseinheit feststellt, dass das Ausmaß der Amplitudenwanderung nicht innerhalb des vorgestimmten, zulässigen Generatorfunktionsgrenzwerts liegt.

30. System nach Anspruch 28, um eine Analyse hinsichtlich konvergenter Nachhalldynamikresonanzen des Ausgabemusters durchzuführen, um von diesem angegebene Mutationen zu identifizieren, ferner umfassend:

    eine Ermittlungseinheit, die betriebsfähig ist, eine erste Gruppe von Resonanzdynamikrelaxationswerten ba-

sierend auf dem tessellierten Ausgabemuster und dem Resonanzstimulus zu bestimmen,

einen Filter, der betriebsfähig ist, die Dynamikrelaxationswerte unter Verwendung von Ensemblegrenz- und CSR-Filtern zu filtern, um eine zweite Gruppe von Werten zu erhalten,

eine Schätzeinheit, die betriebsfähig ist, Masseeigenschaftsschätzfunktionen auf die Dynamikrelaxationswerte anzuwenden, um eine dritte Gruppe von Werten zu erhalten,

eine Evaluierungseinheit, die betriebsfähig ist, die zweiten und dritten Gruppen von Werten zu evaluieren, um zu ermitteln, ob ein vorbestimmter Resonanzkonvergenzgrad erreicht wurde, und

eine Sperrungsdetektionseinheit, die betriebsfähig ist, zu ermitteln, ob eine Dynamiksperrung aufgetreten ist.

31. System nach Anspruch 28, bei dem die Stimuluserzeugungseinheit basierend auf Quantum-Expressor-Funktionen ein Stimulusmuster erzeugt.

32. Verfahren nach einem der Ansprüche 1 bis 27, bei dem ein Ausgabemuster eines Biochips als das Ausgabemuster einer Mikroarrayvorrichtung verwendet wird.

33. System nach einem der Ansprüche 28 bis 31 zum Analysieren eines Ausgabemusters eines Biochips als das Ausgabemuster einer Mikroarrayvorrichtung.

Revendications

1. Procédé d'analyse d'un motif de sortie d'un microdispositif ordonné pour identifier des mutations, le cas échéant, présentes dans un échantillon biologique appliqué au microdispositif ordonné, ledit procédé comprenant les étapes consistant à :

   paver le motif de sortie ;
   générer un motif de stimulus associé à un ensemble de mutations connues ;
   générer un motif de résonance représentatif de résonances entre le motif de stimulus et le motif de sortie pavé ;
   interpréter le motif de résonance pour produire un ensemble de mutations confirmées en comparant les résonances découvertes dans celui-ci à des résonances prédéterminées attendues pour l'ensemble sélectionné de mutations.

2. Procédé de la revendication 1, dans lequel le motif de sortie est issu d'un microdispositif ordonné ayant une pluralité de cellules ayant chacune un ensemble d'oligonucléotides quasiment identiques immobilisés avec les oligonucléotides de chaque cellule étant quasiment uniques par rapport aux oligonucléotides de chaque autre cellule.

3. Procédé de la revendication 1, dans lequel ladite étape de pavage du motif de sortie comprend l'étape consistant à amplifier des variations morphologiques fortement locales dans le motif de sortie.

4. Procédé de la revendication 3, dans lequel le motif de stimulus est généré à partir de fonctions d'expression quantique et dans lequel ladite étape de pavage du motif de sortie est exécutée pour paver le motif de sortie afin qu'il corresponde à des caractéristiques morphologiques des fonctions d'expression quantique.

5. Procédé de la revendication 1 comportant en outre les étapes consistant à :

   extraire une paramétrique locale du motif de sortie pavé ;
   déterminer si un degré de variation d'amplitude représentatif de la paramétrique locale se situe à l'intérieur d'une limite de fonction génératrice autorisée prédéterminée ; et
   sinon, renormaliser le motif de sortie pavé pour qu'il corresponde davantage à des propriétés spectrales du motif de résonance.

6. Procédé de la revendication 5, dans lequel ladite étape d'extraction d'une paramétrique locale du motif de sortie pavé comprend l'étape consistant à extraire des paramètres représentatifs d'une densité d'états intégrée au sein de chacune d'une pluralité de régions de pavage à l'intérieur du motif de sortie pavé.

7. Procédé de la revendication 5, dans lequel un degré de variation d'amplitude est déterminé en appliquant une distribution de Palm afin de développer des générateurs pour estimer une variation stochastique.

8. Procédé de la revendication 1 comportant en outre l'étape consistant à transformer le motif de sortie pavé et le motif de stimulus en un champ aléatoire métriquement transitif.

9. Procédé de la revendication 8 comportant en outre l'étape consistant à renormaliser le motif de sortie pavé après transformation en champ aléatoire métriquement transitif.

10. Procédé de la revendication 9, dans lequel ladite étape de renormalisation est exécutée pour réduire le motif de sortie pavé à l'intervalle [-π, +π].

11. Procédé de la revendication 1, dans lequel l'étape de production d'un motif de stimulus associé à un ensemble de mutations connues comprend les étapes consistant à :

sélectionner un sous-ensemble de mutations pour analyse ; et
sélectionner un sous-ensemble de fonctions d'expression quantique non linéaires à partir d'un ensemble de fonctions d'expression quantique non linéaires prédéterminées sur la base du sous-ensemble de mutations sélectionné.

12. Procédé de la revendication 11 comportant en outre l'étape consistant à transformer les fonctions d'expression quantique non linéaires et le motif de sortie pavé en espace des phases.

13. Procédé de la revendication 1, dans lequel l'étape de production d'un motif de résonance comporte l'étape consistant à traiter par itération le motif de sortie en exécutant une réverbération convergente afin de produire un motif de résonance représentatif de résonances entre un ensemble prédéterminé de fonctions d'expression quantique sélectionnées et le motif de sortie pavé jusqu'à ce qu'un degré prédéterminé de convergence soit atteint entre les résonances découvertes dans le motif de résonance et des résonances attendues pour l'ensemble de mutations.

14. Procédé de la revendication 13, dans lequel l'étape de traitement itératif du motif de sortie par exécution d'une réverbération convergente comporte l'étape consistant à exécuter une analyse de résonance par dynamique réverbérée convergente du motif de sortie pavé à l'aide du motif de stimulus de résonance afin d'identifier des mutations représentées par le motif de sortie pavé.

15. Procédé de la revendication 14, dans lequel l'étape d'exécution d'une analyse de résonance par dynamique réverbérée convergente comporte les étapes consistant à :

a) déterminer un premier ensemble de valeurs de relaxation de la dynamique de résonance à partir du motif de sortie préconditionné et du stimulus de résonance ;
b) filtrer les valeurs de relaxation de la dynamique à l'aide de filtres de limite d'ensemble et CSR afin de produire un second ensemble de valeurs ;
c) appliquer des estimateurs de propriétés grossiers aux valeurs de relaxation de la dynamique pour produire un troisième ensemble de valeurs ;
d) évaluer les second et troisième ensembles de valeurs pour déterminer un degré de convergence de résonance ; et
e) déterminer à partir du degré de convergence de résonance si une paralysie de la dynamique s'est produite et, si c'est le cas, répéter les étapes a) - e).

16. Procédé de la revendication 15, dans lequel ladite étape de détermination de valeurs de relaxation de la dynamique de résonance à partir du motif de sortie préconditionné et du stimulus de résonance comprend l'étape consistant à appliquer un opérateur d'évolution sans convolution au motif de sortie pavé.

17. Procédé de la revendication 15, dans lequel ladite étape d'application d'estimateurs de propriétés grossiers aux valeurs de relaxation de la dynamique pour produire un troisième ensemble de valeurs comprend l'étape consistant à appliquer un opérateur de couplage qui couple les valeurs de relaxation de la dynamique représentatives du motif de sortie pavé à un filtre d'information non linéaire.

18. Procédé de la revendication 15, dans lequel ladite étape d'évaluation des second et troisième ensembles de valeurs pour déterminer un degré de convergence de résonance comprend l'étape consistant à déterminer si le troisième ensemble de valeurs oscille au-delà d'un seuil prédéterminé après une période de temps prédéterminée et, sinon, si une convergence a été atteinte.

19. Procédé de la revendication 18, dans lequel si aucune convergence n'a été atteinte, on exécute l'étape supplémentaire consistant à augmenter l'échelle de temps pour déterminer une convergence au-delà de la période de temps prédéterminée et, si une convergence n'est toujours pas atteinte, on génère alors un signal indiquant qu'aucune des mutations de l'ensemble de mutations n'est présente dans l'échantillon.

20. Procédé de la revendication 15, dans lequel ladite étape consistant à déterminer si une paralysie de la dynamique s'est produite comprend les étapes consistant à évaluer une condition de Lindbald et, si la condition de Lindbald n'a pas été atteinte, générer un signal indiquant qu'une paralysie de la dynamique s'est produite.

21. Procédé de la revendication 20, dans lequel, si une paralysie de la dynamique s'est produite, on exécute les étapes supplémentaires consistant à déterminer si une "mort des mutations" s'est produite en faisant varier l'échelle de temps pour la réalisation de la condition de Lindbald et on répète les étapes en commençant par déterminer les valeurs de relaxation de la dynamique de résonance.

22. Procédé de la revendication 13, dans lequel l'étape de traitement itératif du motif de sortie par exécution d'une réverbération convergente comporte également l'étape consistant à exécuter une analyse de résonance par dynamique réverbérée convergente des mutations à l'aide du motif de stimulus de résonance afin d'identifier des conditions de diagnostic représentées par les mutations.

23. Procédé de la revendication 22, dans lequel l'étape d'exécution d'une analyse de résonance par dynamique réverbérée convergente des mutations à l'aide du motif de stimulus de résonance afin d'identifier des conditions de diagnostic représentées par les mutations comporte les étapes consistant à :

a) déterminer un premier ensemble de valeurs de relaxation de la dynamique de résonance à partir du stimulus de résonance et des mutations ;
b) filtrer les valeurs de relaxation de la dynamique à l'aide de filtres de limite d'ensemble et CSR pour produire un second ensemble de valeurs ;
c) appliquer des estimateurs de propriétés grossiers aux valeurs de relaxation de la dynamique pour produire un troisième ensemble de valeurs ;
d) évaluer les second et troisième ensembles de valeurs pour déterminer si un degré prédéterminé de convergence de résonance a été atteint ; et e) en cas d'absence de convergence, répéter les étapes a) - e).

24. Procédé de la revendication 1 comportant en outre l'étape consistant à filtrer les conditions de diagnostic identifiées par l'analyse de résonance par dynamique réverbérée convergente à partir de propriétés de groupage.

25. Procédé de la revendication 1, dans lequel l'échantillon biologique est choisi dans un groupe constitué par des échantillons d'ADN, d'ARN, de protéine, d'acide peptide-nucléique (PNA) et d'amplification nucléique ciblée (TNA).

26. Procédé de la revendication 1 comportant en outre l'étape consistant à rendre une décision de diagnostic à partir des conditions de diagnostic identifiées par l'analyse de résonance par dynamique réverbérée convergente.

27. Procédé de la revendication 26, dans lequel,
si ladite décision de diagnostic est négative, on détermine alors si une quelconque alternative est disponible ; et
si aucune alternative n'est disponible, on sélectionne un nouveau sous-ensemble de mutations et on répète toutes les étapes.

28. Système d'analyse d'un motif de sortie d'un microdispositif ordonné pour identifier des mutations, le cas échéant, présentes dans un échantillon biologique appliqué au microdispositif ordonné, ledit système comprenant :

une unité de pavage opérant pour paver le motif de sortie ;
une unité de production de motif de stimulus opérant pour générer un motif de stimulus associé à l'ensemble de mutations connues ;
une unité de production de motif de résonance opérant pour générer un motif de résonance représentatif de résonances entre un motif de stimulus et le motif de sortie pavé ;
une unité d'interprétation de motif de résonance opérant pour interpréter le motif de résonance afin de produire un ensemble de mutations confirmées en comparant des résonances découvertes dans celui-ci à des résonances prédéterminées attendues pour l'ensemble sélectionné de mutations.

29. Système de la revendication 28, comprenant en outre :

une unité d'extraction opérant pour extraire une paramétrique locale du motif de sortie pavé ;
une unité de détermination opérant pour déterminer si un degré de variation d'amplitude représentatif de la
paramétrique locale se situe à l'intérieur d'une limite de fonction génératrice autorisée prédéterminée ; et
une unité de renormalisation opérant pour renormaliser le motif de sortie pavé afin qu'il corresponde davantage
à des propriétés spectrales du motif de résonance si l'unité de détermination détermine que le degré de va-
riation d'amplitude ne se situe pas à l'intérieur de la limite de fonction génératrice autorisée prédéterminée.

30. Système de la revendication 28 pour exécuter une analyse de résonance par dynamique réverbérée convergente
du motif de sortie afin d'identifier les mutations représentées par celui-ci, comprenant en outre :

une unité de détermination opérant pour déterminer un premier ensemble de valeurs de relaxation de la dy-
namique de résonance à partir du motif de sortie pavé et du stimulus de résonance ;
un filtre opérant pour filtrer les valeurs de relaxation de la dynamique à l'aide de filtres de limite d'ensemble
et CSR afin de produire un second ensemble de valeurs ;
une unité estimatrice opérant pour appliquer des estimateurs de propriétés grossiers aux valeurs de relaxation
de la dynamique afin de produire un troisième ensemble de valeurs ;
une unité d'évaluation opérant pour évaluer les second et troisième ensembles de valeurs afin de déterminer
si un degré prédéterminé de convergence de résonance a été atteint ; et
une unité de détection de paralysie opérant pour détecter si une paralysie de la dynamique s'est produite.

31. Système selon la revendication 28, dans lequel ladite unité de production de stimulus génère un motif de stimulus
à partir de fonctions d'expression quantique.

32. Procédé selon l'une des revendications 1 à 27, dans lequel un motif de sortie d'une puce à ADN est utilisé comme
le motif de sortie du microdispositif ordonné.

33. Système selon l'une des revendications 28 à 31 pour analyser un motif de sortie d'une puce à ADN comme le
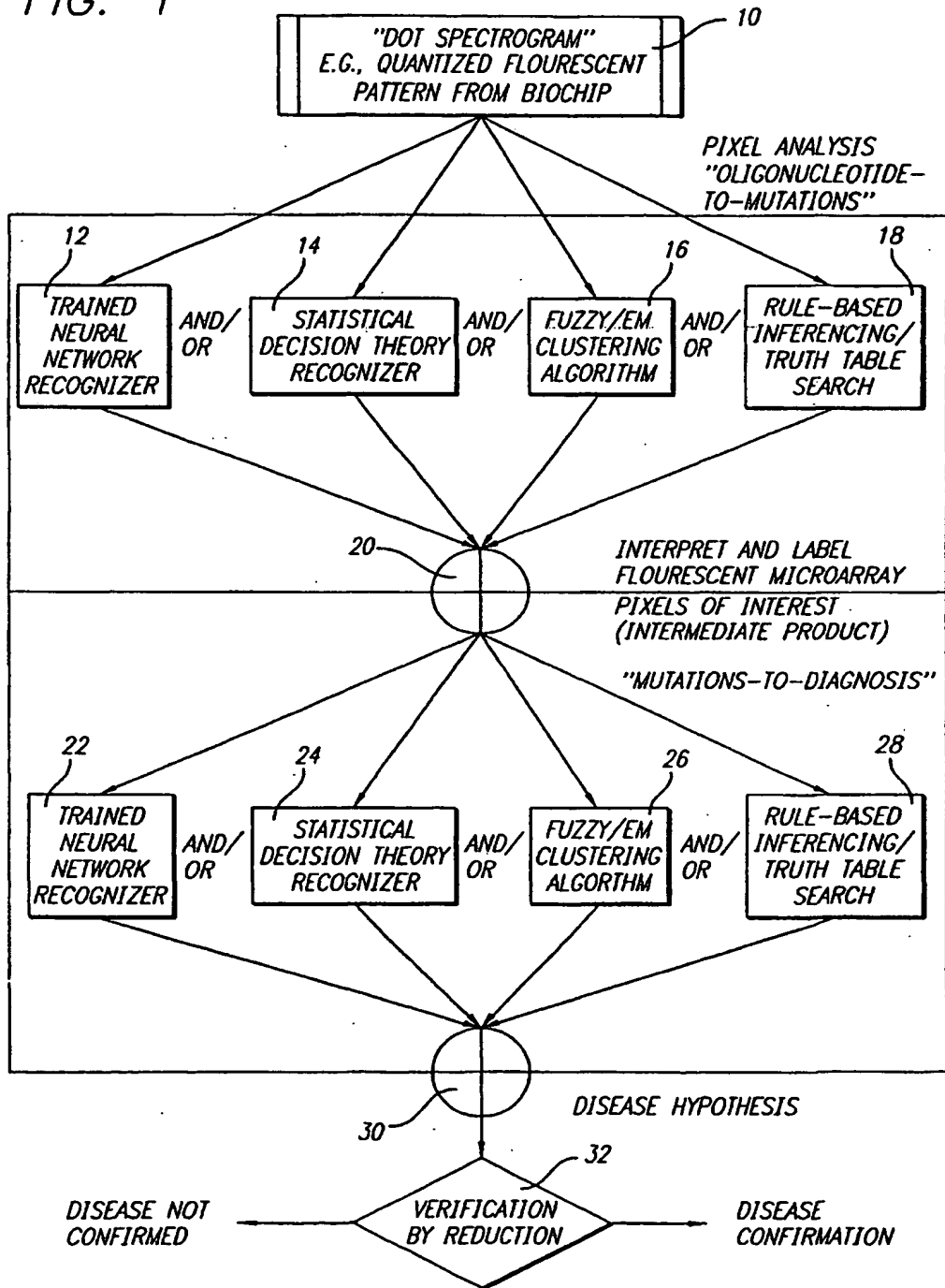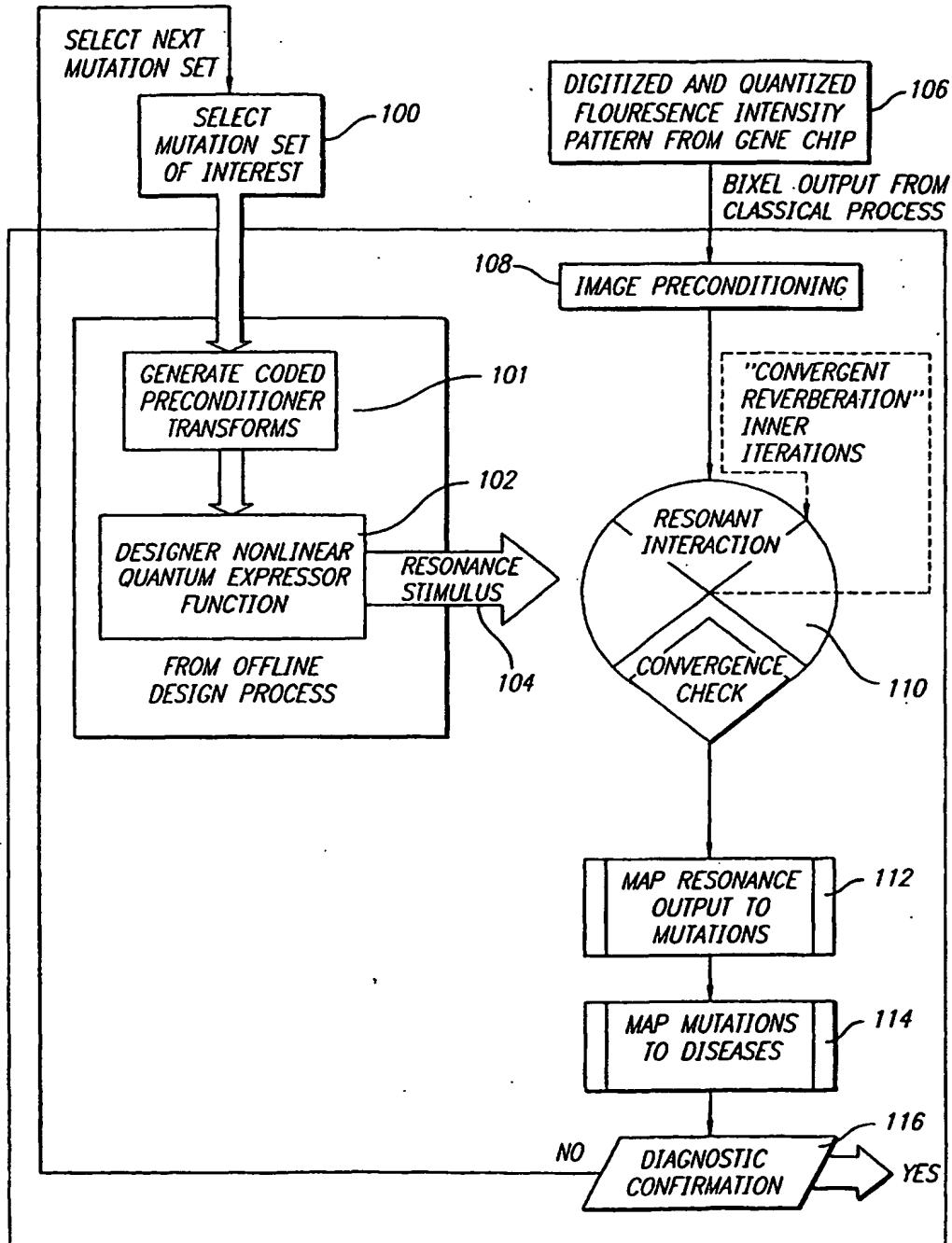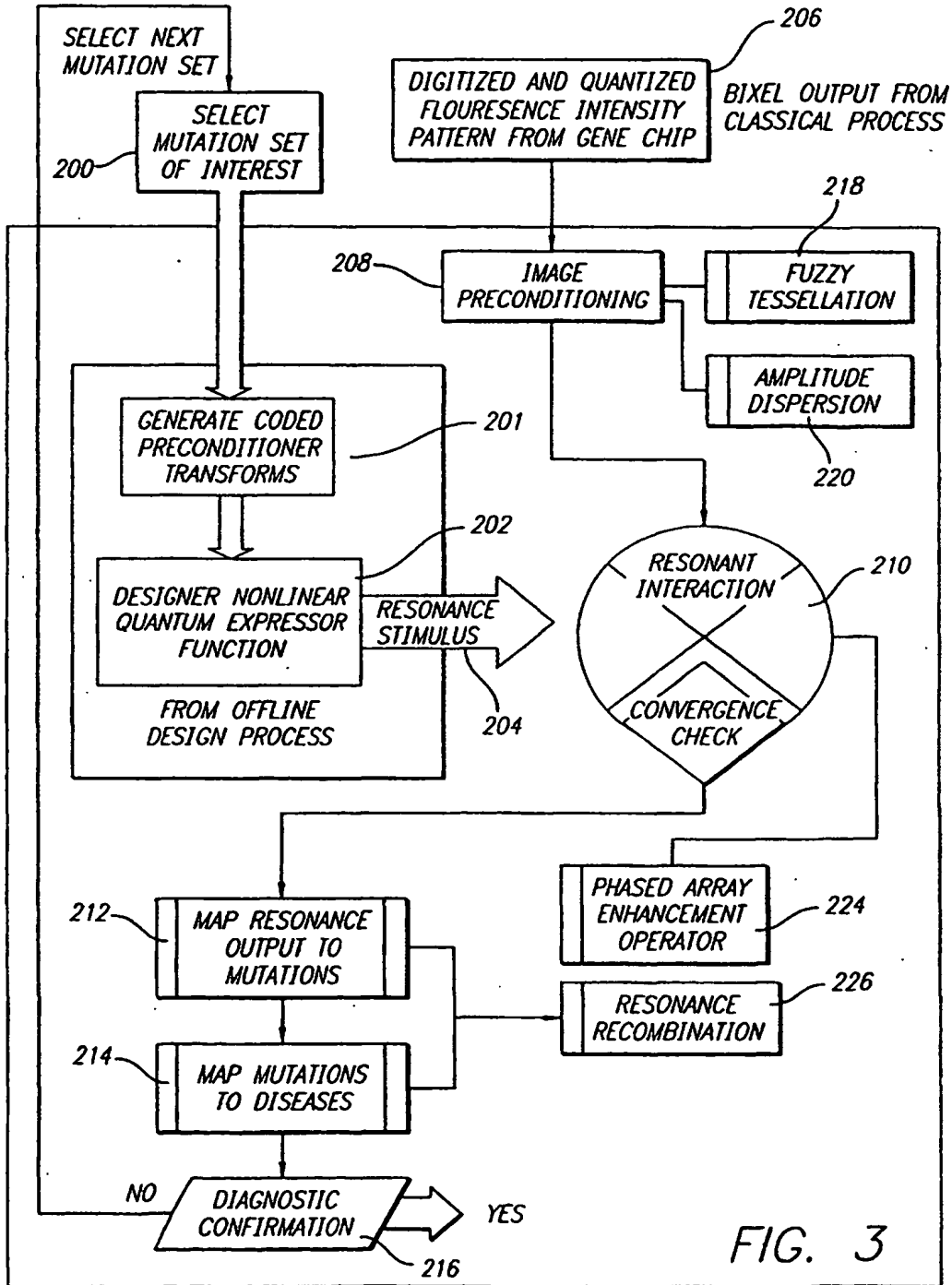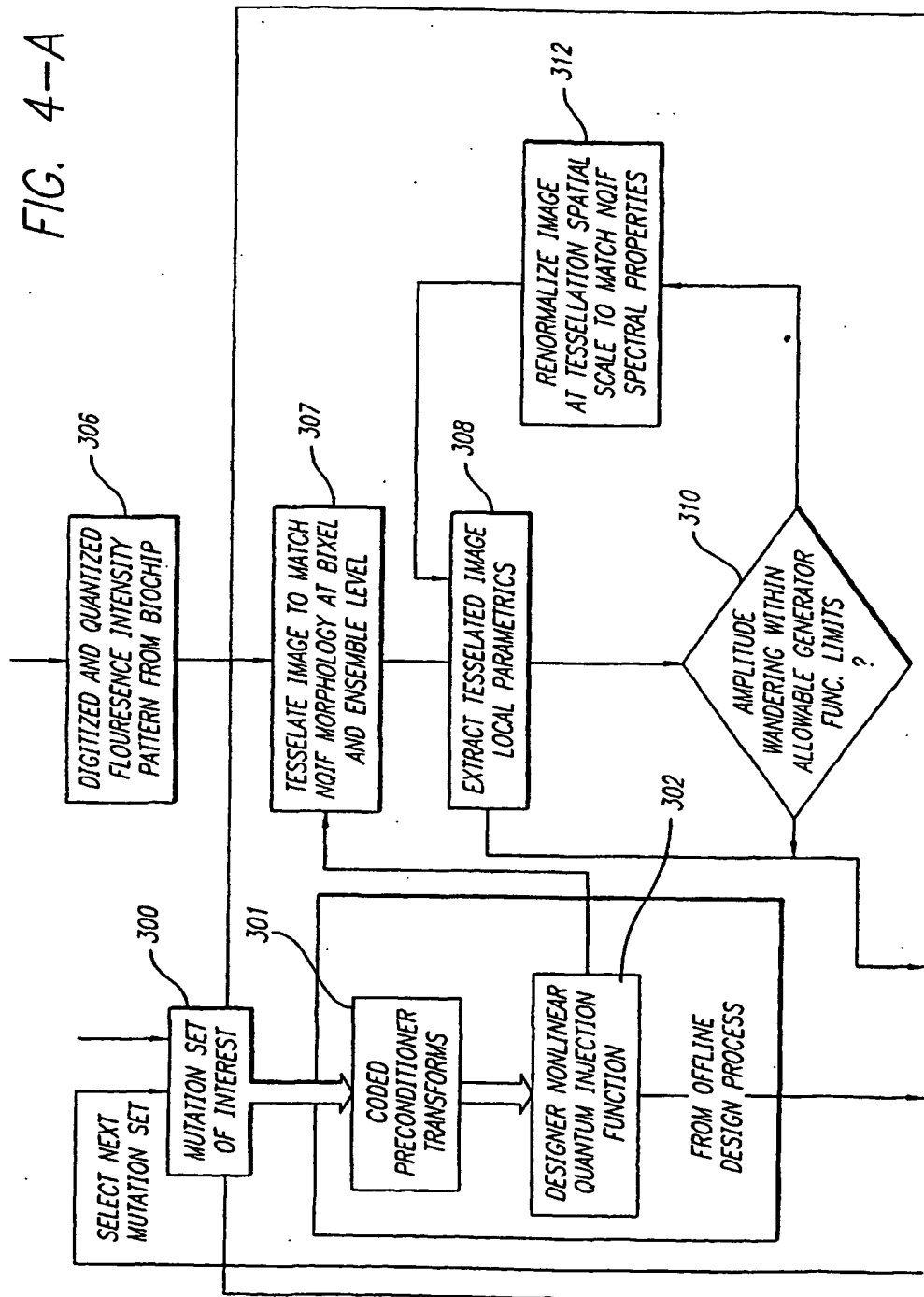motif de sortie du microdispositif ordonné.

FIG. 1

DISEASE NOT CONFIRMED — VERIFICATION BY REDUCTION 32 — DISEASE CONFIRMATION

FIG. 2

FIG. 3

FIG. 4-A

DIGITIZED AND QUANTIZED
FLOURESCENCE INTENSITY
PATTERN FROM BIOCHIP
306

TESSELATE IMAGE TO MATCH
NQIF MORPHOLOGY AT BIXEL
AND ENSEMBLE LEVEL
307

EXTRACT TESSELATED IMAGE
LOCAL PARAMETRICS
308

RENORMALIZE IMAGE
AT TESSELLATION SPATIAL
SCALE TO MATCH NQIF
SPECTRAL PROPERTIES
312

AMPLITUDE
WANDERING WITHIN
ALLOWABLE GENERATOR
FUNC. LIMITS
?
310

SELECT NEXT
MUTATION SET

MUTATION SET
OF INTEREST
300

CODED
PRECONDITIONER
TRANSFORMS
301

DESIGNER NONLINEAR
QUANTUM INJECTION
FUNCTION
302

FROM OFFLINE
DESIGN PROCESS

FIG. 4-B

FIG. 4-C